IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Seo Hong Yoo
Serial No.:	09/778,154
Date Filed:	February 5, 2001
Group Art Unit:	1639
Examiner:	Shibuya, Mark L.
Title:	**PREPARATION OF AQUEOUS CLEAR SOLUTION DOSAGE FORMS WITH BILE SALTS**

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Signature

DECLARATION UNDER 37 C.F.R. § 1.132

Dear Sir:

I, SEO HONG YOO, hereby declare as follows:

1. I am the sole inventor of the invention disclosed and claimed in the above-captioned patent application ("the '154 application").

2. I was a person of at least ordinary skill in the art at the time the invention was made. .

3. Claims 138-148 now pending in the instant application relate to particulate-free aqueous solutions comprising a soluble bile acid and a hydrolytic product of starch.

4. I have reviewed and understand the disclosures of Japanese Patent No. 62153220A to Shinzo Nakazawa and Satoshi Hisano (previously identified as "Satoshi," but hereafter, "Nakazawa") including the professional English translation enclosed herewith as Exhibit A.

FIRST SET OF EXPERIMENTS: CONTROLS

5. Under my direction and control, the following solutions were prepared:

(A) Blanks (BLK)

The solutions listed in Table 1 were prepared for use as reference controls. Some reference controls were prepared to be clear and some were prepared with an expectation that the resulting composition would be turbid or opaque.

Table 1: Reference Controls

BLK-1	distilled water
BLK-2	distilled water
BLK-3	Millipore filtered distilled water
BLK-4	Solution A-1 (this opaque solution contains 800 g of maltodextrin.)
BLK-5	HPLC grade water
BLK-6	ACS reagent water
BLK-7	Millipore filtered distilled water
BLK-8	Solution YS-23-1 (this clear solution contains 60 g of maltodextrin in 100 ml of water)

(B) Invention Solutions

Solutions according the present invention were prepared as described in Table 2.

(C) Invention Solutions

Additional solutions according the present invention were prepared as described in Table 3.

Table 2: Solutions According to the Invention

Solution No.	UDCA	Maltodextrin	Total volume	Method	pH	Ratio*	Date**	Clarity
A-1	-	800 g	1 L				June 11, 2005	opaque
A	**0.3mg**		**200mL**	**MA**	5		June 11, 2005	extremely faintly opalescent
B	25 g	745 g	1 L	**MB**	7	1:29.8	March 20, 2005	visually and instrumentally clear
C	-	-	Alone***					visually and instrumentally clear
D	25 g	745 g	1 L	**MB**	6.54	1:29.8	May 13, 2005	visually and instrumentally clear
E	25 g	745 g	1 L	**MB**	5.26	1:29.8	May 13, 2005	visually and instrumentally clear
F	50 g	312.5 g	1 L	**MB**	7 – 7.2	1:6.25	May 4, 2005	visually and instrumentally clear
G	25 g	745 g	1 L	**MB**	4.5	1:29.8	May 13, 2005	visually and instrumentally clear
H	10 g	-	200 mL		12		June 11, 2005	visually and instrumentally clear
I	25 g	745 g	1 L	**MB**	3.01	1:29.8	May 13, 2005	visually and instrumentally clear
L&M	25 g	300 g	1 L	**MB**	7	1:12	May 4, 2005	visually and instrumentally clear

*** Distilled water was used without additional additives.

****MA: Method of solution A; 5 g of UDCA was dissolved in the solution which contains 0.6g of NaOH to make total 500 ml solution. 0.3 ml of this solution was diluted with distilled water and adjusted pH(5) to make 200 ml of solution A.

*****MB: Method of solution B, D, E, F, G, I and L&M; Solution B, D, E, F, G, I and L&M were prepared in accordance with Example 1 and 3 of the instant application; 25 g (or 50 g) of UDCA and 1 g of preservatives were dissolved in 500 ml of a solution which contains 2.7 g (or 5.4 g) of NaOH . Then, 745 g (or 312.5 g) of maltodextrin was added to make 1L solutions. The pH was adjusted with 20% phosphoric acid to 3.01, 4.5, 5.26, 6.54, 7, and 7-7.2 respectively.

Table 3: Solutions According to the Invention

Solution No.		UDCA	Maltodextrin	Total volume	Date	pH	Ratio*	Clarity
YS-A		20g	120g	400mL	5/4/05	6.55	1:6	visually & instrumentally clear
YS-B		20g	130g	400mL	5/4/05	6.56	1:6.5	visually & instrumentally clear
YS-C		20g	140g	400mL	5/4/05	6.5	1:7	visually & instrumentally clear
YS-D		20g	160g	400mL	5/4/05	6.52	1:8	visually & instrumentally clear
YS-E		20g	200g	400mL	5/4/05	6.55	1:10	visually & instrumentally clear
YS-F		20g	300g	400mL	5/4/05	6.43	1:15	visually & instrumentally clear
YS-G		10g	200g	400mL	5/4/05	6.52	1:20	visually & instrumentally clear
YS-H		5g	150g	400mL	5/4/05	6.45	1:30	visually & instrumentally clear
YS-I		5g	200g	400mL	5/4/05	6.40	1:40	visually & instrumentally clear
YS-J		5g	250g	400mL	5/4/05	6.21	1:50	visually & instrumentally clear
YS-17	Y-17-1	25g	745g	1L	3/20/05	7	1:29.8	visually & instrumentally clear
YS-23	Y-23-1	-	60 g	100 mL	3/20/05	7	-	visually & instrumentally clear
K		20 g	200 g	400 mL	3/20/05	6.55	1:10	visually & instrumentally clear
N		25 g	745 g	1 L	3/20/05		1:29.8	visually & instrumentally clear
U	Y-17-1	25 g	745 g	1 L	3/20/05	7	1:29.8	visually & instrumentally clear
V	Y-17-1	25 g	745 g	1 L	3/20/05	7	1:29.8	visually & instrumentally clear
W	Y-23-1	-	600 g	1 L	3/20/05	7	-	visually & instrumentally clear

*Solution from YS-A to YS-F were prepared in accordance with Example 1 and 3 of the instant application; 20g of UDCA was dissolved in 200 ml of a solution which contains 2.2 g of NaOH . Then, 120 g or 130 g or 140 g or 160 g or 200 g or 300 g of maltodextrin, 0.4 g of preservatives and distilled water were added to make 400 mL solutions. The pH was adjusted with 20% of phosphoric acid to 6.43 – 6.56.

** Solution from YS-G to YS-J were prepared in accordance with Example 1 and 3 of the instant application; 5 g (or 10 g) of UDCA was dissolved in 200 ml of a solution which contains 0.55 g (or 1.1 g) of NaOH . Then, 150 g or 200 g or 250 g (or 200 g) of maltodextrin, 0.4 g of preservatives and distilled water were added to make 400 mL solutions. The pH was adjusted with 20% phosphoric acid to 6.21 – 6.52.

***Solution YS-17, K, N, U and V were prepared in accordance with Example 1 and 3 of the instant application; 25 g (or 20 g) of UDCA and 1 g of preservatives were dissolved in 500 ml of a solution which contains 2.7 g (or 2.2 g) of NaOH . Then, 745 g (or 200 g) of maltodextrin was added to make 1L (or 400 mL) solutions. The pH was adjusted with 20% phosphoric acid to 6.55 - 7.

(D) Nakazawa Solutions

Solutions according Nakazawa were prepared according to the examples as described in the previously submitted English translation (Table 4).

Table 4: Solutions According to Satoshi

Sample No.	Satoshi No.	Description	Observed Clarity	Clarity Claimed by Satoshi
SA-Ex 1	Working Example 1	page 14	Opaque (later, opaque jelly formed)	Clear
SA-1	1	page 11	Opaque (later, opaque mobile liquid)	Clear
SA-2	2	page 11	Opaque (later, opaque mobile liquid)	Clear
SA-3	3	page 11	Opaque (later, opaque mobile liquid)	Clear
SA-4	4	page 11	Opaque (later, opaque mobile liquid)	Clear
SA-5	5	page 11	Opaque(later, opaque mobile liquid)	Somewhat cloudy
SA-6	6	page 11	Suspended (later, settled)	Clear
SA-7	7	page 11	Suspended (later, settled)	Clear
SA-8	8	page 11	Suspended (later, settled)	Cloudy
SA-9	9	page 11	Opaque (later, settled)	Clear
SA-10	10	page 11	Opaque (later, settled)	Clear
SA-11	11	page 11	Opaque (later, settled)	Clear
SA-12	12	page 11	Opaque (later, settled)	Clear
SA-13	13	page 11	Opaque (later, settled)	Cloudy
SA-14	14	page 11	Opaque (later, settled)	Clear
SA-15	15	page 11	suspended (later, settled)	Clear
SA-16	16	page 11	Suspended (later, settled)	Cloudy
SA-17	17	page 11	Opaque (later, settled)	Clear
SA-18	18	page 11	Opaque (later, settled)	Clear
SA-19	19	page 11	Opaque (later, settled)	Clear
SA-20	20	page 11	Opaque (later, settled)	Clear
SA-21	21	page 11	Opaque (later, opaque jelly formed)	Cloudy
SA-22	22	page 11	Suspended (later, settled)	Clear
SA-23	23	page 11	Suspended (later, settled)	Clear
SA-24	24	page 11	Suspended (later, settled)	Cloudy
SA-25	25	page 11	Opaque (later, jelly formed)	Cloudy
SA-30	30	page 11	Opaque (later, settled)	Clear

SA-31	31	page 12	Opaque (later, settled)	Clear
SA-32	32	page 12	Suspended (later, settled)	Somewhat Cloudy
SA-38	38	page 12	Opaque (later, opaque jelly formed)	Cloudy
SA-39	39	page 12	Opaque (later, opaque jelly formed)	Cloudy
SA-40	40	page 12	Opaque (later, opaque jelly formed)	Cloudy
SA-41	41	page 12	Opaque (later, opaque jelly formed)	Clear
SA-42	42	page 12	Opaque (later, opaque jelly formed)	Clear
SA-43	43	page 12	Opaque (later, opaque jelly formed)	Clear
SA-45	45	page 12	Opaque (later, opaque jelly formed)	Cloudy
SA-46	46	page 12	Brownish-opaque (later, opaque jelly formed)	Clear
SA-47	47	page 12	Brownish-opaque (later, opaque jelly formed)	Clear
SA-48	48	page 12	Brownish-opaque (later, opaque jelly formed)	Cloudy
SA-54	54	page 12	Brownish-opaque (not soluble)	Cloudy
SA-55	55	page 12	Brownish-opaque (not soluble)	Cloudy

SECOND SET OF EXPERIMENTS: ABSORBTION

6. Under my direction and control, the clarity of solutions of the present invention were determined. Spectrophotometric analyses were performed using a JASCO V-530 UV/Vis Spectrophotometer in ABS mode with a 2.0 nm band width and medium response. Wavelengths from UV to near infrared were used. Raw absorbance data is presented in Tables 4-11.

Table 4: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm
BLK-1	0.0464	0.0418
L&M	0.9992	0.0697
F	1.1126	0.0767

Table 5: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-2	0.8195	0.0416	0.0019	-0.0027	-0.0015
D	-2.0000	0.0447	0.0092	0.0108	0.0134
B	-2.0000	0.0254	0.0015	0.0025	0.0087
E	-2.0000	0.0135	-0.0099	-0.0107	-0.0086
F	-1.2047	-0.0031	-0.0214	-0.0222	-0.0192
G	0.8237	0.0244	-0.0085	-0.0112	-0.0101

Table 6: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-3	0.0623	0.0578	0.0164	0.0118	0.0129
A-1	3.3305	1.9539	1.6815	1.5866	1.5519
A	3.5119	0.1735	0.0813	0.0699	0.0669
B	3.1065	0.1748	0.0719	0.0458	0.0376
D	3.3452	0.1093	0.0279	0.0216	0.0226
E	3.2982	0.0864	0.0139	0.0081	0.0080
F	1.1302	0.0913	0.0235	0.0172	0.0164
G	3.5441	0.1135	0.0276	0.0194	0.0182
H	0.1582	0.0778	0.0221	0.0161	0.0172
I	3.5520	0.1201	0.0293	0.0186	0.0166

Table 7: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-4	-2.0000	-0.0833	-0.1918	-0.2313	-0.2424
A	-2.0000	-1.8492	-1.7771	-1.7344	-1.7148
C	-2.0000	-1.8964	-1.7906	-1.7430	-1.7204
B	-2.0000	-1.7943	-1.7214	-1.6820	-1.6683
D	-2.0000	-1.8436	-1.7548	-1.7031	-1.6798
E	0.5631	-1.8738	-1.7994	-1.7528	-1.7330
F	-2.0000	-1.9173	-1.8189	-1.7721	-1.7505
G	-2.0000	-1.8910	-1.8251	-1.7781	-1.7571
H	-2.0000	-1.9225	-1.8150	-1.7657	-1.7431
I	-2.0000	-1.8724	-1.7974	-1.7548	-1.7361

Table 8: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-5	0.0123	0.0093	-0.0311	-0.0323	-0.0296
YS-A	1.0008	0.0971	0.0239	0.0164	0.0165
YS-B	1.0663	0.0654	0.0025	-0.0038	-0.0039
YS-C	1.1401	0.0751	0.0069	0.0010	0.0015
YS-D	1.1672	0.0822	0.0124	0.0032	0.0009
YS-E	1.4560	0.0627	-0.0087	-0.0136	-0.0141
YS-F	2.0097	0.0664	-0.0064	-0.0125	-0.0125
YS-G	1.4160	0.0548	-0.0056	-0.0102	-0.0095
YS-H	1.0732	0.0613	0.0042	-0.0013	-0.0008
YS-I	1.4348	0.0800	0.0209	0.0145	0.0147
YS-J	2.1982	0.0918	0.0229	0.0158	0.0154
N	5.0000	0.1387	0.0597	0.0499	0.0479

Table 9: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-6	-2.0000	0.0692	0.0278	0.0228	0.0243
Y-17	-2.0000	0.0609	0.0193	0.0123	0.0124
YS-D	-2.0000	0.0115	0.0183	0.0154	0.0174
YS-E	-2.0000	-0.0085	-0.0036	-0.0052	-0.0030
YS-F	-2.0000	0.0131	0.0203	0.0198	0.0213
YS-G	-2.0000	-0.0259	-0.0129	-0.0136	-0.0116
YS-H	-2.0000	-0.0347	-0.0121	-0.0107	-0.0076
YS-I	-2.0000	-0.0222	-0.0025	-0.0015	0.0018
D	-2.0000	0.0071	0.0047	0.0047	0.0068
E	-2.0000	-0.0001	-0.0011	-0.0001	0.0023
I	-2.0000	0.0333	0.0177	0.0162	0.0168

Table 10: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-7	0.0568	0.0606	0.0191	0.0146	0.0161
Y-23	3.3688	0.1192	-0.0035	-0.0129	-0.0141
Y-17	3.1911	0.1365	0.0326	0.0255	0.0238

Table 11: Absorbance of Solutions According to the Invention

Sample No.	260.0nm	400.0nm	580.0nm	680.0nm	720.0nm
BLK-8	-2.0000	0.0232	-0.0102	-0.0132	-0.0121
Y-17	-2.0000	0.0603	0.0385	0.0341	0.0342
YS-D	-2.0000	-0.0143	-0.0013	-0.0013	0.0015
YS-E	-2.0000	-0.0179	-0.0029	-0.0054	-0.0061
YS-F	-2.0000	0.0299	0.0343	0.0268	0.0264
YS-G	-2.0000	0.0014	0.0188	0.0169	0.0188
YS-H	-2.0000	-0.0075	0.0184	0.0178	0.0203
YS-I	-2.0000	-0.0106	0.0115	0.0104	0.0125
D	-2.0000	0.0094	0.0094	0.0086	0.0106
E	-2.0000	0.0074	0.0077	0.0039	0.0028
I	-2.0000	0.0325	0.0082	0.0020	0.0034

THIRD SET OF EXPERIMENTS: VISUAL INSPECTION

7. Under my direction and control, the clarity of each solution in Paragraph 5 (above) was visually assessed within about two days of preparation. Observations were memorialized in conventional photographs of the samples (Figures 1-121). Figures 1-36 and 107-121 show solutions of the invention along with controls that were either clear (*e.g.*, C-1: distilled water) or turbid (*e.g.*, A-1: maltodextrin alone). Figures 37-78 and 80-106 show compositions prepared according to Nakazawa. In every case, the Nakazawa mixture was clearly not free of particulate matter. In some case, the composition actually formed a gel-like, semi-solid mass. *See* Figure 79. Heating did not clarify the Nakazawa compositions where this was attempted. *See e.g.*, Figures 38, 39, and 43.

8. The foregoing results are wholly consistent with my earlier Rule 132 Declaration dated May 14, 2004 and demonstrate that the disclosures of Nakazawa are insufficient to enable the preparation of bile acid stable, clear solutions. As shown herein and by my earlier declaration, the compositions of Nakazawa were either contaminated with undissolved particles or opaque.

9. Although spectrophotometric measurements were not made of the Nakazawa solutions, visual comparison with the solutions of the invention would be recognized by one of ordinary skill in the art as a proxy for such measurements. For example, Dasta JF *et al.* describe visual inspection as an art recognized means of clarity evaluation and its relationship to spectrophotometric methods. *See* Dasta JF *et al.*, "Comparison of visual and turbidimetric methods for determining short-term compatibility of intravenous critical-care drugs" *Am. J. Hospital Pharm.* (1988) 45:2361-2366. A copy of this document is attached as Exhibit B. Indeed, according to Dasta *et al.*, visual inspection was more sensitive than turbidimetric methods in some cases. *See* Dasta *et al.* at p. 2363, right

column ("Visual grading of precipitation generally corresponded to the absorbance reading s in phase 1; however, 'slight' precipitation was **not** detected turbidimetrically.") (emphasis added).

10. At the time the invention was made, one of ordinary skill in the art would have understood the term "clear" to have a clear and definite meaning. Specifically, one of ordinary skill in the art would have recognized, based in part on the instant specification and Dasta et al., that "clear" means substantially free of precipitate or particles. *See e.g.*, the '154 application, p. 19, lines 9-10.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made may jeopardize the validity of any patent issuing from the above-captioned patent application.

August 2, 2005
Date

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[Translation from Japanese]

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(54) Title of the Invention: **Water-Based Bile Acid Agent for Internal Use**

(21) Patent Application No: 60-292933

(22) Patent Application Date: December 27, 1985

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Clean Copy of Specification (Contents Unchanged)

Specification

1. Title of the Invention

Water-Based Bile Acid Agent for Internal Use

2 Claims

(1) A water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin.

(2) The water-based bile acid agent for internal use described in claim 1, wherein the bile acid is ursodeoxycholic acid or chenodeoxycholic acid.

(3) The water-based bile acid agent for internal use described in claim 2, wherein the dextrin is amylodextrin, maltodextrin or erythrodextrin.

3. Detailed Description of the Invention

Industrial Field of Application

[01] The present invention relates to a water-based bile acid agent for internal use containing a bile acid and a dextrin. The water-based bile acid agent for internal use in the present invention is a clear liquid agent in which the bile acid has been solubilized in water. Because this masks the extreme bitter taste of bile acid solids, it can be used as a bile acid medicine administered orally.

Prior Art

[02] Bile acid is widely used as a cholagogue, a medicine highly valued for its performance and effect. However, bile acid is not very soluble in water and has an extremely bitter taste. Therefore, it has been very difficult to develop a non-bitter bile acid aqueous solution. At the present time, this has hindered the preparation of a water-based agent for internal use that is easier for the digestive tract to absorb than a solid formulation such as a tablet or grains.

[03] Methods of the prior art used to obtain bile acid aqueous solution formulations include solubilizing bile acid in sodium salts (Japanese Examined Patent Application Publication [Kokoku] No. 35-17149) and solubilizing bile acid in clathrate compounds such as β-cyclodextrin (Japanese Unexamined Patent Application Publication [Kokai] No. 55-22616). One method of reducing the bitter taste of bile acid aqueous solutions is to use a sweetener such as sucrose or honey [Basic Course in Drug Development XI: Drug Preparation Methods (Part II), p. 706, Chijinshokan, 15 November 1971].

Problem Solved by the Invention

[04] However, because the solubility method using bile acid salts requires an aqueous solution value between 9.5 and 100, careful pH control is essential and it is difficult to obtain a water-based agent for internal use that is neutral or weakly acidic. In this method, moreover, the bitter taste in the bile acid aqueous solution is not completely eliminated and is sometimes strong. In the solubility

method using clathrate compounds, because the resulting clathrate compounds are bulky (apparent specific gravity 0.04 g/cc, scattering rate 38-45%) and in the form of a fine powder, they are extremely difficult to handle during preparation of the water-based agent for internal use and the scattering of bile acid may have an adverse effect on the health of workers preparing the formulation. The method of reducing the bittor taste of bile acid by using a sweetener also does not completely mask the bitter taste of bile acid in an aqueous solution and leaves an unpleasant aftertaste during oral administration. The bile acid, moreover, is not completely solubilized in syrup containing sucrose or honey, which is a fatal flaw. The present inventors have conducted extensive research on pharmaceutical additives for solubilizing and dispersing difficult-to-solubilize compounds. For example, they have conducted experimental preparation of bile acid aqueous solutions using macromolecular compounds such as sodium carboxymethylcellulose and hydroxypropylcellulose as well as surfactants such as stearic acid polyoxyl 40 and polyethylene glycol. In all of these tests, the solubility and bitter taste masking were never simultaneously adequate.

Means of Solving the Problem

[05] However, when preparing a bile acid aqueous solution using a common dextrin as a binder or formulation diluent, the present inventors surprisingly produced a clear aqueous solution in which the bile acid was completely solubilized and in which there was no bitter taste. The present invention is the product of this discovery.

[06] In other words, the present invention is a water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin (hereinafter referred to as the water-based agent of the present invention).

[07] The amount of bile acid contained in the water-based agent of the present invention can by anywhere within the range of pharmacological effectiveness for bile acid. The amount of dextrin in the water-based agent of the present invention should have a compounding weight ratio of 30:1 or higher with respect to the bile acid and an overall concentration in the water-based agent of 35% (W/W) or less. If (1) the compounding weight ratio is lower than 30:1, the bile acid does not solubilize sufficiently in the water and a water-based bile acid agent cannot be obtained. Furthermore, the bitter taste of the bile acid is not masked sufficiently. If (2) the dextrin concentration exceeds 35% (W/W), the bile acid does not solubilize adequately and the resulting aqueous solution is cloudy. Because an aqueous solution containing dextrin is essentially weakly acidic, the pH of the resulting water-based agent of the present invention can be adjusted relatively easily to obtain a neutral or weakly acidic water-based agent for internal use.

[08] The bile acids that can be used are ursodeoxycholic acid and chenodeoxycholic acid. The dextrins that can be used are amylodextrin, maltodextrin and erythrodextrin.

[09] The essential ingredients of the water-based agent of the present invention are bile acid, dextrin and water. In addition to these three ingredients, other additives can be included during preparation of the agent. These include binding agents such as hydroxypropylcellulose and polyvinylpyrolidone, surfactants such as stearic acid polyoxyl 40, polyoxyothylene-hardened castor oil 60 and propylene glycol, and a small amount of ethanol. Other medicinal additives include preservatives to preserve the bile acid, flavorings and sweeteners. If necessary, supplemental preservatives can be added. Examples of preservatives include butyl paraoxybenzoate, propyl paraoxybenzoate or dehydroacetic acid. Examples of sweeteners include sucrose, glucose, sodium citrate and sodium phosphate. Flavorings include menthol, orange flavoring, strawberry flavoring, vanilla flavoring, liquid cinnamon and plum flavoring. Supplemental preservatives include citric acid, hydrochloric acid and phosphoric acid.

[10] Effective ingredients that supplement the bile acid can be added to the water-based agent of the present invention These include fortifying agents such as γ-olizanol, taurine and royal jelly; vitamins such as thiamine chloride, riboflavin, hydroxine chloride, ascorbic acid, tocophenol, biotin and calcium

pantothenate; and natural medicinals such as gentian, cinnamon, vervain, licorice, ginger, fennel and carrot.

[11] In the water-based agent of the present invention, 1 ppw bile acid and 30 ppw or more dextrin are mixed together in a fluidized bed. While the appropriate amount of binding solution is sprayed on the bed, this mixture is granulized at a circulating warm air temperature of 50-80°C. Water is added, and the grains are stirred and dissolved in the water at a temperature of 15-70°C. The solution can be adjusted at the same temperature using water until the final concentration of dextrin is 35% (W/W) or less. (Hereinafter, this method is referred to as the fluidized-bed granulation method.) An appropriate binding solution is a binding agent such as water or hydroxypropylcellulose and polyvinylpyrolidone or an aqueous solution or ethanol aqueous solution containing a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol. In the granulation stage of the fluidized-bed granulation method, the resulting grains have extremely low scattering properties. In other words, the grains obtained in this manner have an apparent specific gravity 0.35-0.61 g/cc and a scattering rate of 8-13%.

[12] Also, after evenly dispersing 1 ppw bile acid in water, 30 ppw or more dextrin can be added to the dispersant, stirred and dissolved at 15-70°C, and adjusted at the same temperature with water so the final concentration of dextrin is 35% (W/W) or less. (This method is hereinafter referred to as the dispersal method.) In the stage of the dispersal method where the bile acid dispersant is

obtained, the bile acid (apparent specific gravity 0.18-0.25 g/cc, scattering rate 15-24%) can be simply added or dissolved in ethanol to improve the dispersion properties before being added. If necessary, a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol can be added.

[13] Compared to the method of solubilizing bile acid in clathrate compounds (apparent specific gravity 0.04 g/cc, scattering rate 38-44%) (Kokai No. 55-22616), the clear water-based bile acid agents for internal used obtained using the fluidized-bed granulation method and dispersal method pose less risk of scattering bile acid and are easier to handle.

[14] When preservatives, sweeteners, flavorings, supplemental preservatives and other additives are used in the water-based agent of the present invention, they are added in the granulation stage of the fluidized-bed granulation method and in the stage where the bile acid dispersant is obtained in the dispersal method. However, the medicinal additives can be added in the bile acid solubilizing stage of both methods after the bile acid has been stirred and dissolved. If other active ingredients are to be included in the water-based agent of the present invention in addition to bile acid, they too should be added in the bile acid solubilizing stage of both methods. These active ingredients can be added alone or in an aqueous solution or aqueous suspension of vitamins and

nutrients. These can include natural medicinals such as plant extracts, liquid plant extracts, and plant tinctures.

Operation and Effect of the Invention

[15] The following is an explanation of the bile acid solubilizing effect and bitter taste masking effect of dextrin in the water-based agent of the present invention.

[16] In a test of bile acid solubilizing effects and bitter taste masking effects, 70 different samples were prepared and used. In this test, varying amounts of ursodeoxycholic acid (apparent specific gravity 0.24 g/cc, scattering rate 17%) or chenodeoxycholic acid (apparent specific gravity 0.19 g/cc, scattering rate 22%) were dispersed evenly in distilled water, varying amounts of amylodextrin, erythrodextrin or maltodextrin were added, the solution was stirred and mixed at 20-65°C, and the sample was adjusted with water at the same temperature to a total weight of 100 g. The various components in these samples except for the water are shown in the water-based agent composition lines of Table 1 and Table 2. These samples were adjusted so that the pH was between 3.3 and 5.0, that is, weakly acidic.

[17] The bile acid solubilizing effect was determined by measuring the light absorptivity of the samples at 660 nm using a spectrophotometer and by examining the samples with the naked eye to see if they were clear. The bitter taste masking effect was determined in a bitterness taste test with 10 panelists.

[18] The results from the bile acid solubilizing test and bitter taste masking test are shown in Table 1 and Table 2. In the clearness test using the naked eye, + means cloudy, ± means somowhat cloudy, and - means clear. In the bitter taste-masking test, the panelists placed 10 g of each sample in their mouths for 20 seconds to determine if they could taste any bitterness. Here, O means all ten panelists perceived no bitterness, Δ means 1 to 7 panelists perceived some bitterness, and x means 8 or more panelists perceived some bitterness. In both tests, the ratio of dextrin to bile acid in the samples was the significant factor.

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FIG 1

Sample No.		1	2	3	4	5	6	7	8	9	10
Agent Composition	Ursodecxycholic Acid (mg)	12	30	120	200	240	120	200	240	12	25
	Amylodextrin (g)	6	6	6	6	6				15	15
	Maltodextrin (g)						6	6	6		
	Dextrin Concentration % (W/W)	6	6	6	6	6	6	6	6	15	15
	Compounding Ratio	500	200	50	30	25	50	30	25	1250	600
Solubility Effect	Light Absorptivity	0.006	0.008	0.012	0.058	0.302	0.050	0.088	0.497	0.006	0.008
	Clarity	-	-	-	-	±	-	-	+	-	-
Bitterness Masking Effect		O	O	O	O	Δ	O	O	Δ	O	O

FIG 1 (Continued)

Sample No.		11	12	13	14	15	16	17	18	19	20
Agent Composition	Ursodeoxycholic Acid (mg)	250	500	600	250	500	600	60	100	600	1000
	Amylodextrin (g)	15	15	15				30	30	30	30
	Maltodextrin (g)				15	15	15				
	Dextrin Concentration % (W/W)	15	15	15	15	15	15	30	30	30	30
	Compounding Ratio	60	30	25	60	30	25	500	300	50	30
Solubility Effect	Light Absorptivity	0.032	0.084	0.66	0.048	0.092	0.78	0.008	0.010	0.088	0.094
	Clarity	-	-	+	-	-	+	-	-	-	-
Bitterness Masking Effect		O	O	Δ	O	O	Δ	O	O	O	O

FIG 1 (Continued)

Sample No.		21	22	23	24	25	26	27	28	29	30
Agent Composition	Ursodeoxycholic Acid (mg)	1200	600	1000	1200	70	233	437	1167	1750	437
	Amylodextrin (g)	30				35	35	35	35	35	
	Maltodextrin (g)		30	30	30						35
	Dextrin Concentration % (W/W)	30	30	30	30	35	35	35	35	35	35
	Compounding Ratio	25	50	30	25	500	150	60	30	20	80
Solubility Effect	Light Absorptivity	0.89	0.090	0.102	0.98	0.022	0.074	0.088	0.101	1.1	0.100
	Clarity	+	-	-	+	-	-	-	-	+	-
Bitterness Masking Effect		Δ	O	O	Δ	O	O	O	O	Δ	O

FIG 1 (Continued)

Sample No.		31	32	33	34	35	36	37	38	39	40
Agent Composition	Ursodeoxycholic Acid (mg)	1167	1750	80	200	400	500	800	80	200	400
	Amylodextrin (g)			40	40	40	40	40			
	Maltodextrin (g)	35	35						40	40	40
	Dextrin Concentration % (W/W)	35	35	40	40	40	40	40	40	40	40
	Compounding Ratio	30	20	500	200	100	80	50	500	200	100
Solubility Effect	Light Absorptivity	0.102	1.3	0.264	0.62	0.98	1.4	1.5	0.428	0.84	0.96
	Clarity	-	±	=	+	+	+	+	+	+	+
Bitterness Masking Effect		O	Δ	O	Δ	Δ	x	x	O	Δ	x

FIG 2

Sample No.		41	42	43	44	45	46	47	48	49	50
Agent Composition	Chenodeoxycholic Acid (mg)	25	100	250	333	400	250	333	400	60	100
	Amylodextrin (g)	10	10	10	10	10				30	30
	Erythrodextrin (g)						10	10	10		
	Dextrin Concentration % (W/W)	10	10	10	10	10	10	10	10	30	30
	Compounding Ratio	400	100	40	30	25	40	30	25	500	300
Solubility Effect	Light Absorptivity	0.008	0.008	0.022	0.070	0.505	0.040	0.066	0.666	0.010	0.022
	Clarity	-	-	-	-	+	-	-	+	-	-
Bitterness Masking Effect		O	O	O	O	Δ	O	O	Δ	O	O

FIG 2 (Continued)

Sample No.		51	52	53	54	55	56	57	58	59	60
Agent Composition	Chenodeoxycholic Acid (mg)	600	100	1200	1000	1200	70	233	437	1167	1750
	Amylodextrin (g)	30	30	30			35	35	35	35	35
	Erythrodextrin (g)				30	30					
	Dextrin Concentration % (W/W)	30	30	30	30	30	35	35	35	35	35
	Compounding Ratio	50	30	25	30	25	500	150	80	30	20
Solubility Effect	Light Absorptivity	0.094	0.100	0.92	0.098	1.1	0.009	0.048	0.100	0.102	1.2
	Clarity	-	-	+	-	+	-	-	-	-	+
Bitterness Masking Effect		O	O	Δ	O	Δ	O	O	O	O	x

FIG 2 (Continued)

Sample No.		61	62	63	64	65	66	67	68	69	70
Agent Composition	Chenodeoxycholic Acid (mg)	1167	1750	80	200	400	500	800	80	200	400
	Amylodextrin (g)			40	40	40	40	40			
	Erythrodextrin (g)	35	35						40	40	40
	Dextrin Concentration % (W/W)	35	35	40	40	40	40	40	40	40	40
	Compounding Ratio	30	20	500	200	100	80	50	500	200	100
Solubility Effect	Light Absorptivity	0.104	1.4	0.338	0.74	0.98	1.3	1.8	0.56	0.80	1.2
	Clarity	-	+	±	+	+	+	+	+	+	+
Bitterness Masking Effect		O	x	O	Δ	x	x	x	O	Δ	x

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[19] As can be seen in Table 1 and Table 2, the water-based bile acid agents for internal use in which the compounding weight ratio of dextrin to bile acid is 30:1 or higher and in which the dextrin concentration is 35% (W/W) or less are clear aqueous solutions in which the bile acid has been solubilized in the water to a remarkable degree, in which the light absorptivity is less than 0.1, and in which the bitter taste of the bile acid solids has been sufficiently masked. As a result, the water-based bile acid agents of the present invention can be used as non-bitter water-based agents for internal use.

[20] Most of the samples described above correspond to working examples of the present invention. However, in order to explain the present invention further, the following is a description of additional working examples.

Working Example 1

[21] First, 10 g of ursodeoxycholic acid and 1 g of butyl paraoxybenzoate were solubilized in ethanol to obtain exactly 100 ml of solution. Next, 1 ml of the ethanol solution was measured out using a measuring pipette, introduced to 80 g of sterilized water, and dispersed evenly. Next, 3 g of amylodextrin was added to the dispersant and then stirred and mixed evenly at a temperature of 60-65°C. When the amylodextrin was added, the cloudy dispersant immediately became clear and the bitter taste was completely imperceptible.

[22] Next, to the aqueous solution were added 350 mg of licorice extract, 0.8 ml of liquid ginger extract, 1.5 ml of fennel extract, 0.5 ml of liquid cinnamon

extract, 130 mg of carrot extract, 0.1 ml of plum flavoring, 10 g of glucose, and 0.5 g of polyoxyethylene-hardened castor oil 60. The contents were stirred and mixed thoroughly, the solution was passed through a 0.45 μ membrane filter for sterilization filtration, and sterilized water was added to the filtered solution until the total amount was 100 g. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered gastrointestinal agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were 19.8 ± 0.3 mg.

Working Example 2

[23] First, 5 g of chenodeoxycholic acid (apparent specific gravity 0.18 g/cc, scattering rate 24%) and 490 g maltodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 100 g of a 40% (W/W) aqueous ethanol solution containing 1% (W/W) hydroxyproylcellulose into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.41 g/cc and a scattering rate of 10%.

[24] When 32 g of the grains were added to 80 g of sterilized water and mixed in thoroughly, the resulting clear aqueous solution had no bitter taste and was somewhat sweet tasting. Next, 1 ml of an ethanol aqueous solution containing 1% (W/V) butyl paraoxybenzoate and 0.5 g of stearic acid polyoxyl 40 were added to the aqueous solution, stirred and mixed thoroughly, and added to

sterilized water to reach a total weight of 120 g. The resulting solution was divided evenly in four 30 ml drink containers, which were then sealed with metal caps to obtain an orally administered agent. When the amount of chenodeoxycholic acid in each container was measured using gas chromatography, the results were 79.5 ± 0.8 mg.

Working Example 3

[25] First, 5 g of ursodeoxycholic acid (apparent specific gravity 0.25 g/cc, scattering rate 15%) and 395 g erythrodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 80 g of water into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.57 g/cc and a scattering rate of 9%.

[26] When 4 g of these grains were added to 70 g of sterilized water and stirred in thoroughly, a clear aqueous solution was obtained with no bitter taste at all.

[27] Next, to the aqueous solution were added 20 mg of thiamine chloride, 10 mg of tocopherol acetate, 5 mg of riboflavin phosphate, 50 µg of biotin, 1000 mg of taurine, 250 mg of royal jelly, 15 g of sucrose, 0.1 ml of propylene glycol, and 0.1 ml of orange flavoring. After thorough mixing, the solution was adjusted with sterilized water to a total weight of 100 g. The contents were stirred and mixed

thoroughly and the solution was then passed through a 0.45 μ membrane filter for sterilization filtration. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered nutrient enriched agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were 9.9 ± 0.2 mg.

Applicant Tokyo Tanabe Co., Ltd.

Agent Naoyuki MATSUYAMA, Patent Attorney

Amendment of Proceedings (Filed by Applicant)

February 18, 1986

To the Honorable Michio UGA, Director-General of the Japanese Patent Office

1. Application
   Patent Application No. 60-292933

2. Title of the Invention
   Water-Based Bile Acid Agent for Internal Use

3. Party Filing the Amendment
   Relation to Case: Patent Applicant
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6. Section to be Amended: Entire Specification

8. Content of the Amendment: See Attachment
   Clean Copy of Specification (Contents Unchanged)

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Comparison of visual and turbidimetric methods for determining short-term compatibility of intravenous critical-care drugs

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Abstract: Visual and turbidimetric methods for determining the short-term compatibility of critical-care i.v. drugs were compared.

In phase 1, serial dilutions of calcium chloride and magnesium sulfate were examined visually and turbidimetrically to test the sensitivity of the spectrophotometric method used. In phase 2, i.v. solutions of dobutamine, dopamine, lidocaine, nitroglycerin, and nitroprusside were prepared and studied in all possible combinations of two, three, four and five drugs, for a total of 26 different combinations. In phase 3, 45 two-drug combinations previously reported as physically incompatible were studied. Visual inspection was conducted against a dark and a light background; changes were graded as slight, moderate, or gross. Absorbance was determined at 650 nm; an absorbance value of >0.010 was considered to be evidence of turbidity. Visual, turbidimetric, and pH measurements were done at zero, one, and three hours after mixing.

Samples of the calcium chloride-magnesium sulfate mixture that were graded visually as having a slight precipitate had absorbance readings less than 0.010. No physical evidence of incompatibility was observed by either method for dobutamine, dopamine, lidocaine, nitroglycerin, and nitroprusside in any combination. In phase 3, 19 drug combinations were shown to be incompatible; however, only 6 of these (31%) had absorbance readings greater than 0.010 when the visual incompatibility was first observed. There was no physical evidence of incompatibility for several drug combinations that have been listed as incompatible in commonly used references.

Turbidimetry does not appear to be as reliable a method for determining the compatibility of drugs as is visual inspection against a dark and a light background.

Index terms: Additives; Cardiac drugs; Incompatibilities; Injections; Precipitation; Replacement solutions; Stability; Sympathomimetic agents; Tests; Turbidimetry; Vasodilating agents

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Compatibility questions about drugs used in the intensive-care unit (ICU) are particularly difficult for pharmacists to answer since the literature often does not provide answers specifically applicable to this situation.[1] Results of studies reporting an incompatibility at 24 hours, for example, are difficult to apply in the ICU environment. The contact time of drugs administered in the same line to ICU patients is relatively short, even when drugs are administered centrally through a pulmonary artery catheter. For example, one study reported that a colored solution required 28 and 335 seconds to flow through the proximal end of a pulmonary artery catheter at flow rates of 99 and 10 mL/hr, respectively.[2] In addition, the typical ICU patient receives multiple drugs administered intravenously in the same line, whereas most of the literature provides compatibility results only for two-drug combinations.[3,4] These considerations—as well as differing study results because of factors such as formulation differences, pH changes, and adjuvants such as preservatives, stabilizers, and solubilizers—make generalizations difficult.

In many i.v. drug compatibility studies researchers mix drugs in large-volume injectable solutions and visually assess compatibility, using techniques similar to those used in the first systematic study of intravenous drug compatibility published in 1958.[5] The visual methods of determining incompatibility are subjective and nonstandardized. There have not been an adequate number of studies comparing visual techniques with machine-based methods of determining compatibility. We designed this study to evaluate the short-term compatibility of critical-care intravenous drugs, some previously reported to be physically incompatible, and to compare vi-

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sual observations of incompatibility with changes in absorbance recorded by a simple spectrophotometer.

Methods

Phase 1. To compare turbidimetric and visual methods, we used calcium chloride and magnesium sulfate, which are known to form a precipitate when combined. Serial dilutions of calcium chloride injection 100 mg/mL[a] and magnesium sulfate injection 500 mg/mL[b] were prepared, and equal volumes of corresponding dilutions were mixed. The mixtures and controls (sterile water for injection) were coded and randomly arranged by one investigator. Visual inspection and absorbance readings were performed in duplicate in the manner described below.

Phase 2. Intravenous solutions of dobutamine, dopamine, lidocaine, nitroglycerin, and nitroprusside were prepared in the concentrations listed in Table 1. These drugs were mixed and subsequently studied in all possible combinations of two, three, four, and five drugs. This approach resulted in 26 different combinations, with a maximum of five drugs mixed in the same test tube.

Phase 3. Forty-five two-drug combinations, in the concentrations listed in Table 1, were selected for study using the following criteria: (1) any combinations reported to be incompatible when administered as continuous infusions,[3] or (2) any combinations described as incompatible in a reference listing of common ICU drugs,[6] excluding combinations with a reported chemical incompatibility.

General Procedures. Concentrations of drugs in Table 1 were determined based on values commonly used for fluid-restricted patients. Before combining, each drug solution in phases 2 and 3 was inspected visually, and absorbance and pH were de-

Table 1.
Drugs Tested for Compatibility

Drug	Manufacturer	Lot No.	Theoretical Concentration of Admixtures (mg/mL)
Albumin	Hyland	2824D582AA	250
Aminophylline	ESI	106090	4
Ampicillin sodium	Wyeth	2872144	40
Bretylium tosylate	LyphoMed	132614	4
Calcium gluconate	Astra	709128	4
Calcium chloride	Abbott	93-865-DK	4
Cefazolin sodium	Lilly	1CC12A	40
Cimetidine hydrochloride	Smith Kline & French	206T17	6
Diazepam	ESI	096230	0.2
Diazoxide	Schering	6APJ1001	15
Digoxin	ESI	086132	0.005
Dobutamine hydrochloride	Lilly	ORS55A	4
Dopamine hydrochloride	Du Pont Critical Care	7AV403	3.2
Epinephrine hydrochloride	ESI	106112	0.032
Furosemide	ESI	037026	4[a]
Gentamicin sulfate	ESI	116169	3.2
Heparin sodium	ESI	106069	50[b]
Hydralazine hydrochloride	Solopak	870805	1
Insulin (Humulin R)	Lilly	ICZ32A	1[b]
Insulin (beef pork)	Lilly	1DW03A	1[b]
Isoproterenol hydrochloride	ESI	087229	0.032
Lidocaine hydrochloride	Abbott	93-911-DK	8
Magnesium sulfate	LyphoMed	64718	40
Morphine sulfate	Wyeth	2871145	0.2
Nitroglycerin	LyphoMed	16076	0.4
Nitroprusside sodium	ESI	027078	0.4
Norepinephrine bitartrate	Winthrop–Breon	M-210CF	0.032
Pentobarbital sodium	Wyeth	2870086	2
Phytonadione	Merck Sharp & Dohme	1000M	0.4
Potassium chloride	Abbott	04-065-DK	0.08[c]
Propranolol hydrochloride	Ayerst	7DEG1	0.08
Quinidine gluconate	Lilly	ONK40A	6
Sodium bicarbonate	Abbott	91-090-DK	1[c]
Tobramycin sulfate	Lilly	1AX28A	3.2
Verapamil hydrochloride	LyphoMed	850625	0.2

[a] 1 mg/mL for mixtures with dobutamine and hydralazine.
[b] Expressed in units per milliliter.
[c] Expressed in milliequivalents per milliliter.

termined. In a series of Y-injection site studies, Allen et al.[7,8] used a 1:1 ratio of secondary additive and the i.v. admixture. To simulate this situation, equal volumes of drugs were placed into glass test tubes and mixed with a Vortex mixer for 10 seconds. The solution was separated into two tubes. One tube was used to determine evidence of incompatibility, which was defined as a change in color, formation of haze or precipitate, or evolution of gas.[3] Each change was graded as slight, moderate, or gross, using a contrast light with a dark and a light background.[c] The pH of the solution in the other tube was then determined using a pH meter.[d]

A second investigator, who did not know results of the visual compatibility study, used a spectrophotometer[e] to determine the absorbance of light at 650 nm. Solutions were transferred to cuvettes, and the absorbance was determined against a blank of the solution used in the admixture. At 650 nm, the absorbance change reflects the turbidity of the solution and is not affected by color.[9] We considered an absorbance of more than 0.010 to be evidence of turbidity, thus providing a quantitative determination of incompatibility. The specifications of our spectrophotometer suggested that absorbance readings less than 0.010 were considered "noise." Absorbance values greater or less than 0.010 were reported when results of duplicate studies were in agreement.

Drug mixtures in phases 2 and 3 were prepared in 5% dextrose injection[f] and 0.9% sodium chloride injection[g] in Viaflex i.v. bags. Ampicillin was diluted only in 0.9% sodium chloride injection.[g] Albumin and diazoxide injections were used undiluted; diazepam, hydralazine, and nitroglycerin injections were prepared in sterile glass evacuated bottles.[h] Nitroprusside, hydralazine, and phytonadione solutions were protected from light with aluminum foil. Studies in all phases were performed in duplicate, on separate days, at ambient laboratory temperature and under constant fluorescent lighting. Visual, pH, and turbidimetric observations were made at zero, one, and three hours after mixing.

Results

In all cases, the results of each run of the duplicate studies were in agreement. The results of the phase 1 study are shown in Table 2. Visual grading of precipitation generally corresponded to the absorbance readings in phase 1; however, "slight" precipitation was not detected turbidimetrically. We found no evidence of incompatibility in phase 2 for the five drugs tested in any combination, and all absorbance readings were less than 0.010. Drug combinations listed in Table 3 showed no evidence of incompatibility, and all absorbance readings were less than 0.010. Table 4 lists those drug combinations found to be incompatible. Absorbance readings taken when incompatibility was first observed visually were above 0.010 for only six combinations (31%). Except for albumin and verapamil, all combinations with high absorbance readings were visually graded "gross." Albumin was the only drug studied that was turbid alone. The designation "incompatible" for albumin and verapamil was based on an increase in haze during the observation period. No consistent pH changes above 0.5 were seen in duplicate samples of any combination studied, whether compatible or not.

Discussion

This study provides some useful information about the compatibility of several i.v. drugs used in ICUs. The most striking finding was the lack of evidence of incompatibility for the large number of drug combinations in Table 3 that have been listed as incompatible in commonly used refer-

Table 2.
Visual Observations versus Absorbance Readings for Mixture of Calcium Chloride and Magnesium Sulfate

Dilution	Study 1		Study 2	
	Visual	Absorbance	Visual	Absorbance
Undiluted	Gross	2.000	Gross	2.000
1:2	Gross	1.977	Gross	1.957
1:4	Gross	1.886	Gross	1.949
1:8	Moderate	0.010	Moderate	0.033
1:16	Slight	0.004	Slight	−0.003
1:32	Slight	0.000	Slight	−0.005
1:64	None	−0.005	None	0.000
1:128	None	−0.005	None	−0.001
1:256	None	−0.004	None	0.002
1:512	None	−0.003	None	−0.001
1:1024	None	0.000	None	−0.003
Control[a]	None	0.003	None	−0.001
Control[a]	Slight	−0.009	Slight	−0.001

[a] Sterile water for injection.

Table 3.
Drug Combinations Showing No Physical Evidence of Incompatibility over Three Hours

1.	Aminophylline	+	cimetidine
2.	Aminophylline	+	morphine
3.	Ampicillin	+	calcium gluconate[a]
4.	Ampicillin[b]	+	phytonadione
5.	Bretylium	+	isoproterenol
6.	Cefazolin	+	calcium gluconate
7.	Cefazolin	+	lidocaine
8.	Diazepam	+	quinidine
9.	Dobutamine	+	bretylium
10.	Dobutamine	+	calcium chloride
11.	Dobutamine	+	calcium gluconate
12.	Dobutamine	+	diazepam
13.	Dobutamine	+	furosemide[a]
14.	Dobutamine	+	heparin[a]
15.	Dobutamine	+	insulin[c]
16.	Dobutamine	+	magnesium sulfate
17.	Dobutamine	+	potassium chloride
18.	Dobutamine	+	verapamil
19.	Epinephrine	+	calcium chloride
20.	Epinephrine	+	calcium gluconate
21.	Epinephrine	+	phytonadione
22.	Epinephrine	+	furosemide
23.	Hydralazine	+	nitroglycerin[d]
24.	Insulin[c]	+	sodium bicarbonate
25.	Insulin[c]	+	digoxin[a]
26.	Morphine	+	calcium chloride
27.	Morphine	+	sodium bicarbonate
28.	Morphine	+	heparin
29.	Pentobarbital	+	norepinephrine
30.	Pentobarbital	+	insulin[c]
31.	Quinidine	+	heparin[a]
32.	Verapamil	+	hydralazine

[a] In 0.9% sodium chloride injection only.
[b] Ampicillin in 0.9% sodium chloride injection.
[c] Both Humulin R and Iletin I.
[d] In 5% dextrose injection only.

ences.[3,6] Review of the original studies revealed several possible reasons for the discrepancy between literature reports and our findings. For combinations 9–11 and 15–18 in Table 3, a pink color was reported at 24 hours.[10,11] These studies involved dobutamine, which can develop a pink color when the aliphatic amino side chain is oxidized.[12] The reported pink color may have been caused by the oxidation of dobutamine alone, rather than a reaction between the drugs in combination. The new formulation of dobutamine solution used in this study contains an antioxidant that should minimize this problem. In another study, a haze was reported with dobutamine and magnesium sulfate beginning at 20 hours, which is considerably longer than our study period.[13] For drug combinations 7, 8, 12, 15, and 32 in Table 3, drug concentrations different from those in this study were used.[4,11,14,15] For example, when dobutamine was mixed with regular insulin in a concentration 50-fold greater than that used in this study,[14] a white precipitate was reported within 30 minutes.

Drug combinations 2, 24, and 27–30 in Table 3 were reported incompatible in a 1966 study in which the authors mixed a drop from each of two drug solutions and made observations with a microscope.[16] Drug concentrations were not provided; hence, they may have differed from those used in our study. Also, drug formulations, such as that of insulin, have changed over the past 20 years. Morphine plus heparin and aminophylline plus cimetidine have been found to be compatible.[7,17,18] References for eight drug combinations (1, 3, 4, 6, and 19–22 in Table 3) provided insufficient information about the study methods for comparison.[3,4,19]

For some combinations, an explanation of the disparate findings was more difficult. For dobutamine and furosemide in 0.9% sodium chloride injection, cloudiness at 1 hour and immediate precipitation have been reported in two studies.[10,15] The drug concentrations examined in these studies were similar to ours; however, the authors used different brands of furosemide and the previously available dobutamine formulation. For quinidine and heparin, a precipitate has been reported.[4] Although the concentrations used were similar to ours, the reference is in the form of a personal communication from 1973, and no further information is provided. We found no evidence of incompatibility between dobutamine and heparin in 0.9% sodium chloride injection. Since variable reports of precipitation have appeared in the literature, caution should be used in combining these drugs.[20] No primary reference could be found for the remaining three drug combinations (5, 25, and 26) in Table 3.[6]

For combinations 1, 3, 4, 7–9, 11–16, and 19 in Table 4, we confirmed, and in some cases further quantified, reports of incompatibility.[4,10,11,14,21–24] For the remaining six combinations in Table 4, we could not find a primary reference source for the reported incompatibility.[6]

Since the average patient receives almost eight different drugs during an ICU stay, it is possible that more than two drugs will be combined in the same line.[25] Except for total parenteral nutrient solutions, most of the literature on i.v. compatibility reports results only for two-drug admixtures.[3,4] One cannot conclude that multidrug combinations will be compatible even if each drug pair is compatible individually. Except for sodium nitroprusside, for which no compatibility information was available, all other drugs tested in phase 2 were reported to be compatible in two-drug combinations.[10,13,26,27]

Chemical compatibility was not evaluated. Alterations in chemical structure can occur without physical changes.[28] The likelihood of any important chemical change was minimized by the short contact time in this study, since the extent of drug degradation is time dependent.

Turbidimetry was selected as a method of analysis to assess its ability to minimize problems associ-

Table 4.
Drug Combinations Showing Physical Evidence of Incompatibility

	Drug Combination			Solution	Time[a] (hr)	Visual Observation	Absorbance
1.	Albumin	+	verapamil	D5W[b]	1	Slight haze	>0.010
	Albumin	+	verapamil	NS[c]	3	Slight haze	>0.010
2.	Ampicillin	+	calcium gluconate	D5W	1	Slight color	<0.010
3.	Ampicillin	+	epinephrine	D5W/NS	3	Slight color	<0.010
4.	Calcium chloride	+	sodium bicarbonate	D5W	1	Slight haze	<0.010
	Calcium chloride	+	sodium bicarbonate	NS	1	Slight ppt[d]	<0.010
5.	Diazoxide	+	propranolol	D5W	1	Moderate ppt	<0.010
					1	Slight color	<0.010
	Diazoxide	+	propranolol	NS	3	Moderate ppt	<0.010
6.	Digoxin	+	insulin	D5W	1	Slight haze	<0.010
7.	Dobutamine	+	aminophylline	NS	1	Slight ppt	<0.010
					1	Slight color	<0.010
	Dobutamine	+	aminophylline	D5W	1	Slight haze	<0.010
					1	Slight color	<0.010
8.	Dobutamine	+	furosemide	D5W	1	Slight ppt	<0.010
9.	Dobutamine	+	heparin	D5W	0	Gross ppt	>0.010
10.	Dobutamine	+	phytonadione	D5W/NS	3	Slight haze	<0.010
11.	Furosemide	+	quinidine	D5W/NS	0	Gross ppt	>2
12.	Heparin	+	gentamicin	D5W/NS	0	Gross haze	>0.010
13.	Heparin	+	quinidine	D5W	0	Gross haze	>0.010
14.	Heparin	+	tobramycin	D5W/NS	0	Gross haze	>0.010
15.	Hydralazine	+	aminophylline	D5W	1	Gross color	<0.010
	Hydralazine	+	aminophylline	NS	3	Slight haze	<0.010
					1	Moderate color	<0.010
16.	Hydralazine	+	ampicillin	D5W	1	Moderate color	<0.010
	Hydralazine	+	ampicillin	NS	3	Moderate color	<0.010
17.	Hydralazine	+	diazoxide	D5W/NS	1	Moderate ppt	<0.010
					1	Moderate color	<0.010
18.	Hydralazine	+	furosemide	D5W/NS	3	Slight color	<0.010
19.	Hydralazine	+	nitroglycerin	NS	3	Slight ppt	<0.010

[a] Time when incompatibility was first recorded.
[b] D5W = 5% dextrose injection.
[c] NS = 0.9% sodium chloride injection.
[d] Precipitation.

ated with the more subjective visual inspection methods. A turbid solution should result in changes in absorbance that could be quantitated in a more objective manner than visual estimates of incompatibility. However, turbidimetry was not able to consistently detect changes that were observed visually. There are several possible explanations for this inconsistent performance. First, the wavelength set for the determination of turbidity is above the value required to detect color. Thus, this method will not detect color changes that develop during the study. Also, the single beam of light passed through the cuvette may miss a precipitate if it settles to the bottom of the container. Finally, detection of slight degrees of precipitation may require a more sophisticated instrument than the one used in this study. Although we cannot recommend this technique, perhaps others can be developed to overcome some of the inadequacies of this system.

Because of the numerous factors affecting compatibility, our results should be interpreted within the framework of the methods of this study. For example, these data would not necessarily be applicable to other drug concentrations or formulations, or when questions of long-term compatibility arise. These findings do suggest that other drug combinations previously reported to be incompatible and other multiple (more than two) drug combinations need to be evaluated.

Conclusion

Turbidimetry does not appear to be as reliable a method for determining the compatibility of drugs as is visual inspection against a dark and a light background.

[a] Abbott Laboratories, North Chicago, IL 60064, lot 93-855-DK.
[b] LyphoMed, Inc., Rosemont, IL 60018, lot 64718.
[c] Vesco Intravenous Solution Visual/Clarity Inspection Station, Vesco Instruments, Inc., Plainview, NY 11803.
[d] Model 470A Ionalyzer, Orion Research, Inc., Cambridge, MA 02139.
[e] Model 340 Sequoia-Turner Corp., Mountain View, CA 94043.
[f] Baxter, Inc., Deerfield, IL 60015, lot ZP011478.
[g] Baxter, lot ZP011478.
[h] Baxter, lot G775866.

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Watching for New Viruses

Our preoccupation with acquired immunodeficiency syndrome should not obscure the multiplicity of infectious diseases that threaten our future. It is none too soon to start a systematic watch for new viruses before they become so irrevocably lodged. The fundamental bases of virus research can hardly be given too much encouragement. Recombinant DNA, still a scare word in some quarters, is our most potent means of analyzing viruses and developing vaccines. Such research should be done on a broad international scale to both share the progress made in advanced countries and amplify the opportunities for field work at the earliest appearance of outbreaks in the most afflicted areas. . . .

As one species, we share a common vulnerability to these scourges. No matter how selfish our motives, we can no longer be indifferent to the suffering of others. The microbe that felled one child in a distant continent yesterday can reach yours today and seed a global pandemic tomorrow. "Never send to know for whom the bell tolls; it tolls for thee."

—Lederberg J. Medical science, infectious disease, and the unity of humankind. *JAMA*. 1988; 260:684–5.